



## Complete Summary

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### **GUIDELINE TITLE**

The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a clinical practice guideline.

### **BIBLIOGRAPHIC SOURCE(S)**

Ellis P, Davies AM, Evans WK, Haynes AE, Lloyd NS, Lung Cancer Disease Site Group. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Oct 18. 47 p. (Evidence-based series; no. 7-14-1). [133 references]

### **GUIDELINE STATUS**

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

## **COMPLETE SUMMARY CONTENT**

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## **SCOPE**

### **DISEASE/CONDITION(S)**

Advanced malignant pleural mesothelioma

### **GUIDELINE CATEGORY**

Assessment of Therapeutic Effectiveness  
Treatment

**CLINICAL SPECIALTY**

Oncology  
Pulmonary Medicine

**INTENDED USERS**

Physicians

**GUIDELINE OBJECTIVE(S)**

- To evaluate if palliative chemotherapy improves quality of life or symptom control in patients with advanced malignant pleural mesothelioma
- To evaluate if palliative chemotherapy improves survival in patients with advanced malignant pleural mesothelioma
- To evaluate which chemotherapeutic agents (or combinations of agents) have shown the highest response rates

**TARGET POPULATION**

Adult patients with advanced, symptomatic malignant pleural mesothelioma who have a good performance status (Eastern Cooperative Oncology Group 0-1) and are not suitable for surgical resection

**INTERVENTIONS AND PRACTICES CONSIDERED**

1. Non-platinum-based single agent chemotherapy (considered but not recommended)
2. Non-platinum-based combination chemotherapy (considered but not recommended)
3. Platinum-based single-agent (not recommended) or combination chemotherapy (pemetrexed or raltitrexed plus cisplatin)
4. Chemotherapy plus immunotherapy (considered but not recommended)

**MAJOR OUTCOMES CONSIDERED**

- Response rate
- Survival (progression-free, overall)
- Time to progression
- Time to treatment failure
- Quality of life (QOL)
- Symptom control

**METHODOLOGY**

**METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

## **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

Evidence was identified through a systematic search of MEDLINE (1966 through October 2005), EMBASE (1980 through October 2005), CANCERLIT (1966 to March 2002), and the Cochrane Library databases (2005, Issue 3). Search terms used included "mesothelioma", (Medical subject heading (MeSH) and Excerpta Medica Tree (EMTREE) term) with and without the subheading "drug therapy", combined with "drug therapy" (MeSH), "chemotherapy, adjuvant" (MeSH), and "antineoplastic agents" (MeSH), "chemotherapy" (EMTREE), "adjuvant therapy" (EMTREE), and the text word "mesothelioma". Those terms were combined with the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, phase II or III clinical trials, and multicenter or comparative studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) for the years 1997-2005 were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

### **Inclusion Criteria**

Articles published as full reports or as abstracts were selected for inclusion in this systematic review of the evidence if they were:

1. Practice guidelines, systematic reviews, or meta-analyses evaluating the use of chemotherapy for malignant pleural mesothelioma (MPM).
2. Randomized clinical trials (RCTs) comparing chemotherapy with best supportive care (BSC), or different chemotherapy regimens.
3. Phase II clinical trials evaluating chemotherapy, either as single agents or combinations of agents.
4. Phase II clinical trials evaluating chemotherapy (single-agent or in combination) combined with immunotherapies such as interferon and interleukin, and if they met the following criteria:
5. Study population included patients with MPM. Studies including patients with both pleural and peritoneal malignant mesothelioma were also eligible.
6. Outcomes of response, survival, quality of life (QOL), or symptom control were reported.

### **Exclusion Criteria**

The following were excluded from the systematic review:

1. Papers published in a language other than English.
2. Clinical trials primarily assessing immunotherapies.
3. Trials of chemotherapy combined with surgery and/or radiation therapy.

The literature search for phase II trials was not updated after April 2002 as there were data from large randomized trials on which to make treatment recommendations.

## **NUMBER OF SOURCE DOCUMENTS**

113 articles were included

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

## **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

As the chemotherapy regimens involved were heterogeneous, the results of the randomized trials were not pooled. A decision was made to group the phase II trials according to the following major categories: single-agent chemotherapy, non-platinum combinations, single-agent platinum agents, combination platinum agents, and chemotherapy plus immunotherapy. The response rates of the noncomparative trials were pooled by the formula  $PRR = \sum(w_i RR_i) / \sum w_i$ , where PRR is the pooled response rate of the studies,  $w_i$  is the weight of the  $i^{th}$  study, and  $RR_i$  is the response rate of the  $i^{th}$  study. RR was calculated by dividing the proportion of complete or partial responses by the total number of patients in a study. 'w' was determined by the inverse of the variance for a study, with the variance calculated by multiplying the proportion of patients with a complete or partial response with the proportion of patients with no response and then dividing the result by the total number of patients in the study. The 95% confidence interval (95% CI) for each PRR was calculated by the formula  $PRR \pm 1.96SE_{PRR}$ , where  $SE_{PRR} = \sqrt{1/\sum w_i}$ .

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

No identified trials directly answered the question of whether chemotherapy improves survival or quality of life (QOL) for patients with malignant pleural mesothelioma (MPM) compared with best supportive care (BSC). Weak evidence from several of the phase II trials existed to show that chemotherapy produced symptom improvement in some patients with MPM. Additionally, data from one large randomized trial showed improved survival and QOL for combination compared with single-agent chemotherapy. Therefore, the consensus of the Lung Disease Site Group (DSG) was that there was sufficient evidence to support the use of combination chemotherapy with cisplatin and pemetrexed for patients with symptomatic MPM who have good performance status (Eastern Cooperative Oncology Group [ECOG] 0-1). Vitamin supplementation with vitamin B<sub>12</sub> and folic acid is an essential component of chemotherapy treatment with pemetrexed and cisplatin as supplementation substantially improves the toxicity profile of the chemotherapy regimen.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

### **External Review by Ontario Clinicians**

Following review and discussion of sections 1 and 2 of this evidence-based series, the Lung Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 141 practitioners in Ontario (35 medical oncologists, 22 radiation oncologists, 27 surgeons, and 57 respirologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on November 13, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

### **Practice Guidelines Coordinating Committee (PGCC) Approval Process**

The evidence summary report was circulated to 15 members of the PGCC for review and approval. Seven of 15 members of the PGCC returned ballots. One PGCC member is also a Lung DSG member and as such indicated on their ballot that they were not eligible to review the evidence summary report. Four PGCC members approved the evidence summary report as written. One member approved the evidence summary report with a comment for consideration by the Lung DSG. Another member approved the report conditional on the Lung DSG addressing specific concerns.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Despite many reports on the use of chemotherapy in the palliative treatment of malignant pleural mesothelioma, only a limited amount of high-quality evidence exists on which to base recommendations. Based on this limited evidence, the Lung Cancer Disease Site Group instead makes the following observations and offers the following opinions:

The strongest evidence supports the use of pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> every 3 weeks, with vitamin supplementation with B<sub>12</sub> 1000 micrograms monthly and folic acid 0.4-1.0 mg daily and is recommended for the palliative treatment of adult patients with advanced malignant pleural mesothelioma. Both vitamin supplements should be started before the administration of pemetrexed.

If pemetrexed is not available then there is weaker evidence to recommend the use of raltitrexed 3 mg/m<sup>2</sup> and cisplatin 80 mg/m<sup>2</sup> every three weeks.

The routine substitution of carboplatin for cisplatin is not recommended.

Given the very limited amount of high-quality evidence on the role of chemotherapy in malignant pleural mesothelioma, patients should be encouraged to participate in clinical trials of treatment for this disease.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials, non-comparative studies, and meta-analyses.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- One large randomized trial comparing chemotherapy with pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> every three weeks to cisplatin alone demonstrated improved survival and quality of life for the two-drug combination versus single agent cisplatin. That trial included 448 eligible patients randomized to either single-agent cisplatin or the combination regimen. Response rates (41% versus 17% respectively,  $p < 0.001$ ), time to progression (5.7 versus 3.9 months,  $p = 0.001$ ), and survival (12.1 versus 9.3 months, hazard ratio 0.77,  $p = 0.02$ ) all favoured combination treatment.
- Two quality-of-life indices (dyspnea and pain) assessed using the Lung Cancer Symptom Scale were significantly improved with pemetrexed and cisplatin after six cycles of treatment ( $p = 0.004$  and  $p = 0.017$ , respectively).
- A second trial randomised 250 patients to either raltitrexed plus cisplatin, versus cisplatin alone. This trial demonstrated a significant improvement in overall survival (11.4 versus 8.8 months, hazard ratio [HR]=0.76,  $p = 0.048$ ). This trial also showed a higher response rate (23.6% versus 13.6%,  $p = 0.056$ ) and longer progression free survival (5.3 versus 4 months,  $p = 0.058$ ), although these differences did not achieve conventional statistical significance.
- There are no trials of chemotherapy versus Best Supportive Care. However, the opinion of the Lung Cancer Disease Site Group is that single-agent cisplatin, the control arm for both the randomized trials, is unlikely to reduce survival in this patient population. Thus, the opinion of the Lung Cancer Disease Site Group is that the above trials provide sufficient indirect evidence that pemetrexed and cisplatin combination chemotherapy will improve survival and quality of life for these patients, and is therefore, recommended.
- One hundred eleven noncomparative phase II trials were identified that examined chemotherapy for patients with malignant pleural mesothelioma. The pooled response rates for trials examining platinum-containing regimens as single agents (14.3%, 9 trials) or in combination with other agents (24.9%, 19 trials) are higher than the pooled response rates for trials examining nonplatinum-containing regimens as single agents (3.6% to 9.0%, 51 trials) or in combination (10.4%, 12 trials).
- Data from eight noncomparative phase II trials indicate that the pooled response rates to single-agent carboplatin are less than cisplatin (10.1% versus 20.0%).

## POTENTIAL HARMS

One large randomized trial comparing chemotherapy with pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> every three weeks to cisplatin alone demonstrated grades 3 and 4 toxicity were higher with the combined treatment: neutropenia (28% versus 2%), thrombocytopenia (6% versus 0%), vomiting (13% versus 4%), and febrile neutropenia (2% versus 0%).

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician.

Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Quick Reference Guides/Physician Guides

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

End of Life Care  
Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

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### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2005 Oct 18

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]



## **GUIDELINE DEVELOPER COMMENT**

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

## **SOURCE(S) OF FUNDING**

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

## **GUIDELINE COMMITTEE**

Provincial Lung Cancer Disease Site Group

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

The members of the Lung Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this evidence summary. One of the lead authors and two Disease Site Group members reported membership on an advisory board of Eli Lilly, the pharmaceutical company that manufactures pemetrexed (Alimta®). Two Disease Site Group members reported additional involvement with Eli Lilly, including research involvement, research funding, provision of consultancy and expert testimony, ownership interests, or receipt of honoraria.

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Oct 18. Various p. (Practice guideline; no. 7-14-1: Section 1). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This summary was completed by ECRI Institute on May 29, 2007. The information was verified by the guideline developer on June 22, 2007.

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